Prevention of Hepatic Veno-occlusive Disease After Bone Marrow Transplantation by Continuous Infusion of Low-Dose Heparin: A Prospective, Randomized Trial

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Hepatic veno-occlusive disease (VOD) is a major regimen-related toxicity after bone marrow transplantation (BMT). Endothelial injury, leading to deposition of coagulation factors within the terminal hepatic venules, is believed to be the key event in the pathogenesis of VOD. To evaluate the benefit and the safety of a VOD prophylaxis with anticoagulants, we conducted a prospective randomized trial of continuous infusion of low-dose heparin among 161 patients undergoing either allogeneic (n = 79) or autologous BMT (n = 81). Patients were randomized to receive (n = 81) or not receive (n = 80) prophylactic heparin 100 U/kg/d by continuous infusion from day −8 until day +30 post-BMT. Heparin was found to be highly effective in preventing VOD, which occured in 11 of 80 patients (13.7%) in the control group versus 2 of 81 (2.5%) in the heparin group ($P < .01$). Furthermore, none of the 39 patients in the heparin group developed VOD after allogeneic BMT, versus 7 of 38 (18.4%) in the control group ($P < .01$). This prophylactic effect was achieved without added risk of bleeding. Indeed, the low-dose heparin we used did not prolong the partial thromboplastin time and did not increase the red blood cell and platelet requirements. It is therefore recommended that heparin prophylaxis be part of early mortality prevention programs after BMT.

VENO-OCCLUSIVE disease of the liver (VOD) has been defined as a narrowing or fibrous obliteration of terminal hepatic venules and small lobular veins.[1,2] It is the third leading cause of transplantation-related death, after graft-versus-host disease (GVHD) and infections, in patients undergoing allogeneic bone marrow transplantation (BMT), and the second leading cause after infections in patients undergoing autologous BMT.[3] The reported incidence of VOD after BMT is about 20%, with a mortality rate of 50%.[3-5]

Early reports showed that the primary cause of VOD after BMT was chemotherapy and radiotherapy used to prepare patients for transplantation.[2,6-8] Several additive factors have been identified: age, underlying disease, the type of conditioning regimen, and hepatitis or known metastatic liver disease before BMT.[2-4,9-11] The mechanisms and cellular events resulting in VOD are much less understood. Endothelial damage, due to the conditioning regimen, is believed to be the key event in the pathogenesis of VOD.[12-16] This endothelial injury triggers the coagulation cascade and induces the deposition of coagulation factors in the adventicial and subendothelial zones of the affected venules.[17] The resulting obstruction of hepatic venous outflow probably induces additional damage to hepatocytes surrounding the terminal venules.

Because hepatocellular necrosis that leads to patient death does not occur until several days after initial endothelial injury, it was reasonable to speculate that prophylactic anticoagulant therapy might preserve venous outflow, and ultimately hepatic function. Two reports of uncontrolled studies lend credence to this approach, because in these two studies a low incidence of VOD was observed in patients treated with prophylactic heparin after BMT.[18,19]

The impact of such a prophylactic effect of heparin would be considerable in the BMT setting. Indeed, once VOD is clinically apparent there is no proven effective medical therapy,[5] despite occasional reports of successful outcome after treatment with recombinant tissue plasminogen activator[20] or prostaglandin E_1.[21] Therefore, a controlled trial was warranted to test the efficacy and safety of VOD prophylaxis with heparin after BMT. We report here the first trial designed to address these crucial issues. One hundred sixty-one patients were randomized to receive or not receive continuous infusion of low-dose heparin for the prevention of VOD after either autologous or allogeneic BMT.

PATIENTS AND METHODS

Requirements for patient enrollment. All patients admitted to the BMT unit of Purpan hospital from January 1988 to September 1991, who were to receive unpurged autologous or non–T-depleted HLA genoidentical allogeneic BMT prepared with standard regimens, were eligible for this study. Standard regimens included: (1) cyclophosphamide (CY) (120 mg/kg) and total body irradiation (TBI) (12 Gy); (2) CY (120 mg/kg) and busulfan (BU) (16 mg/kg); (3) melphalan (MEL) (140 mg/m^2) and TBI (8 Gy); (4) CY (6 g/m^2), etoposide (1 g/m^2), and carmustine (300 mg/m^2) (CBV). Patients were excluded if they had lesions at risk of bleeding (eg, recent history of peptic ulcer disease). We also excluded patients with a history of deep venous thrombosis. According to the criteria stated above, 16 patients were excluded for the following reasons: one patient with recent deep venous thrombosis, one patient with recent peptic ulcer disease, six patients who had received nonstandard preparative regimens, five patients who had received a mismatched allogeneic BMT, and three patients who had received a matched unrelated allogeneic BMT. Informed consent was obtained either from patients or from one of their parents in accordance with institutional policy.

Patients. One hundred sixty-one patients were enrolled in the study. Their clinical characteristics are detailed in Table 1. Mean age was 36.1 years (range, 1 to 65). Seventy-seven patients received allogeneic BMT, 82 received autologous BMT, and two received syngeneic BMT. Patients were treated for the following diseases: 32 for acute myelogenous leukemia (AML), 31 for acute lympho-

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Table 1. Clinical Characteristics of the Treatment Groups

Characteristics	Heparin Group	Control Group	Total
No. of patients	81	80	161
Sex (M/F)	55/26	47/33	102/59
Mean age in years (SD)	36.3 (14.4)	35.9 (14)	36.1 (14)
Diagnosis			
AML (all/1st CR/ > 1st CR)	17/14/3	15/12/3	32/26/6
ALL (all/1st CR/ > 1st CR)	15/13/2	16/11/5	31/24/7
CML (all/chronic/phase/others)	18/11/7	12/6/6	30/17/13
Myeloma (all/1st response/ ≤ 1st response)	16/11/5	17/11/6	33/22/11
Lymphoma (all/1st response/ > 1st response)	13/3/10	16/5/11	29/8/21
Aplasia	2	4	6
Mean interval between diagnosis and BMT in months (SD)	12.8 (14.3)	16.1 (21.7)	14.4 (18.4)
Type of graft			
Allogeneic	39	38	77
Syngeneic	1	1	2
Autologous	41	41	82
Preparative regimen			
CY-TBI	31	31	62
MEL-TBI	14	16	30
BU-CY	25	19	44
CBV	11	14	25
Pretransplant hepatitis B serology			
Hbs Ag^- and anti-Hbs Ag^-	73	70	143
Hbs Ag^- and anti-Hbs Ag^+	8	10	18
Hbs Ag^+	0	0	0
Pretransplant CMV serology			
Positive	37	32	69
Negative	44	48	92
Pretransplant SGOT value			
≤40 IU	68	76	144
>40 IU	10	7	17
Pretransplant bilirubinemia value			
≤19 μmol/L	79	75	154
>19 μmol/L	2	5	7

None of the characteristics differed significantly between treatment groups.

blastic leukemia (ALL), 33 for multiple myeloma, 29 for malignant lymphoma, and six for severe aplasia. Seventeen patients (10%) had an abnormal aspartate amino-transferase value (SGOT) before BMT (laboratory norms, <40 IU). Seven patients (4%) had abnormal total serum bilirubin before BMT (laboratory norms, <19 μmol/L). None of the patients had positive serology for hepatitis B antigen before BMT. Sixty-nine patients (43%) had positive serology for cytomegalovirus before BMT.

Study design. Ten days before transplantation, patients were randomized to receive or not receive prophylactic heparin. The treatment allocation for each patient was assigned via telephone by the biostatistics department, which had prepared before initiation of the trial a computer-generated sequence unknown to the physicians participating in the trial. Randomization was stratified according to the type of graft (allogeneic/autologous). Prophylactic 100 U/kg/d heparin was administered by continuous intravenous infusion, starting on the day preparative therapy began until 30 days posttransplant or until patients were discharged from the sterile unit (whichever occured first). Activated partial thromboplastin time (APTT) was determined twice a week on blood samples collected from a lumen of a double-lumen Hickman right atrial catheter that was never flushed with heparin. The dose of heparin was not adjusted according to the results of APTT. Heparin was intended to be discontinued for any major bleeding episode. Major bleeding was defined as bleeding in the central nervous system, bleeding associated with hemodynamic instability, or an unexplained decrease in hematocrit levels.

VOD evaluation. Patients were classified as "suspicion of VOD" when at least two of the following features were found before day 30 after transplant[4]: (1) bilirubinemia greater than 34 μmol/L; (2) ascites or weight gain greater than 5% of baseline value; (3) development of hepatomegaly and right upper quadrant pain evaluated by clinical examination and confirmed by echography.

Patients with "suspicion of VOD" were classified as "clinical VOD" if no other identifiable cause of liver disease was present. Patients with "suspicion of VOD" with another cause of liver disease underwent transjugular liver biopsy and were classified according to histologic results.

Patients with "clinical VOD" that did not improve after day 30 postgraft underwent transjugular liver biopsy and/or postmortem examination. They were classified as VOD according to histologic findings. Patients with "clinical VOD" that resolved before day 30 after BMT did not undergo liver biopsy. They were classified as VOD.

All available liver histologies were blindly reviewed by one of us (J.-J.V.). VOD was considered present if the terminal hepatic venules or small sublobular veins had concentric subendothelial thickening and luminal narrowing by either edematous reticulum fibers or collagen.[2]

BMT procedure. Preparative regimens are detailed in Table 1. Ninety-two patients received a TBI-containing regimen (57%), 44 patients received a BU-CY regimen (27%), and 25 patients received the CBV regimen (16%). Patients received autologous unpurged cryopreserved graft or non–T-depleted genoidentical

allogeneic graft on day 0. Prevention of GVHD was attempted by the administration of methotrexate plus cyclosporin.[22] Patients were treated in laminar air-flow or positive-pressure rooms with usual aseptic precautions.[23] All patients received sterile diet. A total gut decontamination regimen with oral nonabsorbable antibiotics (cephalosporin, gentamicin, bacitracin) was started on day 8 before BMT. Patients received fluconazole for prophylaxis of fungal infections, acyclovir for prevention of herpes infections, and ranitidine for prophylaxis of upper gastrointestinal tract bleeding. Blood products were irradiated before transfusion. Neither prophylactic nor therapeutic granulocyte transfusion was used. Central venous catheters were inserted surgically, 1 week before admission to the sterile unit.

Clinical variables analyzed. The 11 pretransplant characteristics listed in Table 1 were analyzed to compare the two treatment arms and for their effect on the subsequent development of VOD. These factors are generally self-explanatory. "Early disease" included AML and ALL in first complete response, myeloma and lymphoma in first response, and chronic myelogenous leukemia (CML) in first chronic phase. "Advanced disease" was used for other phases of malignant disease. Hepatic encephalopathy was diagnosed in patients with neurologic dysfunction in the setting of hepatic failure, when either an elevated serum ammonia was present or when no other cause for the neurologic dysfunction could be found. Renal toxicity was defined as a twofold or more increase in baseline serum creatinine. A patient was defined to be refractory to platelet transfusions if the platelet count remained below the pretransfusion level 24 hours after platelet transfusions during 5 consecutive days. Day 0 was the day of BM infusion. The day of resolution of VOD was defined as the day the bilirubin improved to 19 μmol/L or less.

Statistical analysis. The proportions of patients with a given characteristic were compared by χ^2 test or Fischer's exact test. Differences in the means of continuous measurements were tested with Student's *t*-test controlled by nonparametric Mann-Whitney U test. All tests were two-sided. The study was designed to compare the proportions of patients with VOD during the first month post-BMT. A minimum of 80 patients assigned randomly to each treatment arm was required to ensure a significance level of 5% and a power of 95% if the true VOD rates were 2% and 15%. The study was completed by an enrollment of 161 patients.

RESULTS

Randomization. Eighty-one patients were randomly assigned to the heparin group and 80 patients to the control group. As shown in Table 1, patient characteristics of each group were similar, and no significant differences were found with regard to age, sex, underlying disease, type of graft, preparative regimen, pre-BMT serology of hepatitis B and cytomegalovirus (CMV), and pre-BMT value of SGOT and bilirubin.

VOD during the first month post-BMT. Table 2 shows the number of patients in each group with elevated bilirubin, weight gain greater than 5%, or hepatomegaly.

In the control group, 14 patients (17.5%) had at least two of these clinical features and were classified as "suspicion of VOD" (see Patients and Methods). Two of the 14 patients with "suspicion of VOD" had cutaneous GVHD, and transjugular liver biopsy confirmed hepatic GVHD without VOD. Thus, 12 patients (15%) were classified as "clinical VOD" (see Patients and Methods). Eight of the 12 patients with "clinical VOD" underwent transjugular liver biopsy and/or postmortem examination. VOD was histologically confirmed in seven of eight patients, but could not be validated in one of eight patients (nonspecific hepatitis with massive hemochromatosis). Four of the 12 patients with "clinical VOD" were considered as VOD without histologic examination (see Patients and Methods). Therefore, 11 of 80 patients (13.7%) were classified as VOD that occurred at a mean of 13.5 days (SD 4.3) after BMT in the control group (Table 2).

Table 2. VOD During the First Month Post-BMT

	Heparin Group (n = 81)	Control Group (n = 80)	*P*
No. of patients with bilirubinemia ≥34 μmol/L (%)	6 (7.4)	15 (18.7)	<.05
No. of patients with weight gain ≥5% (%)	12 (14.8)	26 (32.5)	<.05
No. of patients with hepatomegaly (%)	4 (4.9)	17 (21.2)	<.01
No. of patients with at least two of the VOD clinical features (%)	3 (3.7)	14 (17.5)	<.01
No. of patients with at least two of the VOD clinical features without other cause for liver disease	2 (2.4)	12 (15)	<.01
Histologic results for patients with clinical VOD			
Not available	0	4	
VOD	2	7	
Non-VOD	0	1	
No. of patients with final diagnosis of VOD			
All patients (%)	2 (2.5)	11 (13.7)	<.01
Autologous and syngeneic BMT (%)	2 (4.7)	4* (9.5)	NS
Allogeneic BMT (%)	0 (0)	7† (18.4)	<.01
Time of onset of VOD, mean day post-BMT (SD)	25 (4.2)	13.5 (4.3)	<.01
No. of patients who died with VOD (%)	2/81 (2.5)	7/80 (8.8)	NS

Abbreviation: NS, not significant.
*One of four was histologically confirmed.
†Six of seven were histologically confirmed.

In the heparin group, three patients (3.7%) had at least two of the VOD clinical features and were classified as "suspicion of VOD." One of the three patients with "suspicion of VOD" had cutaneous GVHD, and transjugular liver biopsy confirmed hepatic GVHD associated with chronic viral hepatitis without VOD. Thus, two patients (2.5%) were classified as "clinical VOD." These two patients underwent liver biopsy that confirmed VOD. Therefore, 2 of 81 patients (2.4%) were classified as VOD in the heparin group (Table 2). VOD occured in these two patients on days 28 and 22 post-BMT. However, in these two patients, heparin administration had been interrupted before the onset of VOD, because of discharge from the sterile unit (days 20 and 17 post-BMT, respectively).

Thus, the prophylactic use of heparin was found to be highly effective in preventing VOD during the first month post-BMT ($P < .01$) (Table 2).

Bleeding during the first month post-BMT. A full course of heparin was administered in 77 of 80 patients. The median duration of this full course after BMT was 26 days (range, 17 to 30). Heparin was discontinued before day 10 in three patients because of poor platelet increments after transfusion associated with minor gastrointestinal bleeding. No major bleeding occured in the heparin group. The highest value of APTT was not affected by heparin administration: median, 41.2 seconds (SD 6.4) in the heparin group versus 41.3 seconds (SD 17.1) in the control group. The number of red blood cell transfusions was not significantly different between the treatment groups: mean, 6.9 (SD 3.8) in the heparin group versus 7.3 (SD 4.3) in the control group. As shown in Table 3, the mean duration of thrombocytopenia, the mean number of platelet transfusions, and the number of patients refractory to platelet transfusions were not significantly different between the treatment groups.

BMT-related toxicity during the first month postgraft. As shown in Table 3, the mean duration of neutropenia, the mean number of days with fever (38°C or more), and the incidence of septicemia were not affected by heparin administration. The incidence of severe GVHD was similar in two groups. Twenty-four patients developed a renal toxicity: seven were enrolled in the heparin group and 17 in the control group ($P < .05$). However, in patients without VOD, the administration of heparin did not decrease the incidence of renal dysfunction (Table 3). Thus, the lower incidence of renal dysfunction in the heparin group appears to be related to the decreased incidence of VOD.

Table 3. Clinical Results During the First Month Post-BMT

	Heparin Group (n = 81)	Control Group (n = 80)	P
Highest activated PTT in seconds, mean (SD)	41.2 (6.4)	41.3 (17.1)	NS
No. of red blood cell transfusions, mean (SD)	6.9 (3.8)	7.3 (4.3)	NS
Mean duration of thrombocytopenia (<25,000/mm³) in days (SD)	18.2 (10.5)	19.6 (12.1)	NS
No. of platelet transfusions, mean (SD)	9.2 (7.4)	10.3 (8.3)	NS
No. of patients refractory to platelet transfusions (%)	22 (27.2)	28 (35)	NS
Mean duration of neutropenia (<500/mm³) in days (SD)	20 (9.2)	18.7 (7.4)	NS
No. of days with fever (above 38°C), mean (SD)	4.4 (3.7)	4.7 (4.2)	NS
Septicemia*			
Gram-positive (%)	3 (3.7)	9 (11.2)	
Gram-negative (%)	4 (4.9)	5 (6.2)	
Total (%)	7 (8.6)	14 (17.5)	NS
Acute GVHD			
Grade 0-1 (%)	24 (61.5)	20 (52.6)	NS
Grade ≥2 (%)	15 (38.5)	18 (47.4)	NS
No. of patients with 100% increase in baseline serum creatinine			
All patients (%)	7 (8.6)	17 (21.2)	<.05
Patients without VOD (%)	5 (6.3)	10 (14.5)	NS
Day 100 survival (%)			
All patients	75/81 (92.6)	71/80 (88.7)	NS
Autologous and syngenic BMT	40/42 (95)	41/42 (97.6)	NS
Allogenic BMT	35/39 (89.7)	30/38 (79)	NS

Abbreviation: NS, not significant.
*Two or more positive blood cultures.

Table 4. Clinical Features Associated With VOD (n = 13)

Time of onset of VOD, mean day post-BMT (range)	15 (5-28)
No. of patients with hepatomegaly (%)	13 (100)
Highest value of bilirubinemia (μmol/L), median (range)	61 (30-209)
Highest weight gain (%), median (range)	10 (6-16)
No. of patients with ascite (%)	8 (61.5)
Highest value of SGOT (IU), median (range)	85 (33-1,755)
No. of patients with 100% increase in baseline serum creatinine (%)	9 (69)
No. of patients requiring hemodialysis	1
No. of patients with encephalopathy	6
No. of patients refractory to platelet transfusions (%)	11 (84)
Outcome	
Resolved (%)	4 (30.7)
Death with VOD (%)	9 (69)

Characteristics of patients with VOD. The clinical features of the 13 patients with VOD are detailed in Table 4. Four patients had resolution of their VOD at a median of 29 days after BMT. Nine patients died with persistant hepatic dysfunction (2 of 81 in the heparin group *v* 7 of 80 in the control group; P = NS). Two died of unrelated causes (relapse) and seven died before day 60 post-BMT of multiple organ failure, with liver disease playing a major part (bleeding due to hepato-cellular insufficiency, two cases; interstitial pneumonia, two cases; aspergillosis, two cases; septicemia, one case).

Eleven of the 13 patients with VOD (84%) were found to be refractory to platelet transfusions during the first month post-BMT. VOD caused a significant increase in the platelet transfusion requirements: mean 15.9 (SD 6.8) in the VOD group versus 9.2 (SD 7.7) in the non-VOD group ($P < .01$). Various clinical characteristics were analyzed for the effect on the development of refractoriness to platelet transfusions in the 161 patients included in this trial. Clinical variables tested were age, sex, diagnosis, interval between diagnosis and BMT, preparative regimen, septicemia, GVHD, and VOD. Two variables reached a significant level in the univariate analysis: (1) severe GVHD versus moderate or absent GVHD (13 of 32 patients *v* 3 of 44 patients, respectively; $P < .001$); and (2) VOD versus non-VOD (11 of 13 patients *v* 39 of 144 patients, respectively; $P < .0001$).

We analyzed the effect of 12 pretransplant characteristics on the posttransplant development of VOD. As shown in Table 5, the absence of heparin and a diagnosis other than ALL or lymphoma were predictive for VOD in the univariate analysis.

Table 5. Frequency of VOD by Pretransplant Characteristics

Characteristic	Frequency (%)	P
Age		
< 15 yr	0/12	NS
≥ 15 y	13/149	
Sex		
Male	8/102 (7.8)	NS
Female	5/59 (8.5)	
Type of graft		
Allogeneic	7/77 (9.1)	NS
Autologous + syngeneic	6/84 (7.1)	
Diagnosis		
AML	3/32 (9.4)	
ALL	1/31 (3.2)	
CML	5/30 (16.7)	
Lymphoma	0/29	
Aplasia	0/6	
Myeloma	4/33 (12.1)	NS
ALL + lymphoma/other malignancy	1/60 (1.7)/12/83 (12.6)	<.05
Status of disease		
Early phase	6/97 (6.1)	
Advanced phase	7/58 (12.1)	NS
Preparative regimen		
TBI-CY	4/62 (6.5)	
TBI-MEL	3/30 (10)	
BU-CY	6/44 (13.6)	
CBV	0/25	NS
Interval diagnosis-BMT		
≤ 12 mo	8/114 (7)	
> 12 mo	5/47 (10.6)	NS
Pre-BMT anti-Hbs Ag		
Positive	2/18 (11.1)	
Negative	11/143 (7.7)	NS
Pre-BMT CMV serology		
Positive	6/69 (8.7)	
Negative	7/92 (7.6)	NS
Pre-BMT SGOT		
≤ 40 IU	13/144 (9)	
> 40 IU	0/17	NS
Randomization		
With heparin	2/81 (2.5)	
Without heparin	11/80 (13.7)	<.01

Abbreviation: NS, not significant.

DISCUSSION

BMT-related mortality has decreased significantly during the last few years.[24] However, the early mortality associated with allogeneic BMT is still about 30%.[24] GVHD,[25] infections,[26] and VOD[3] are the main contributing factors to early mortality. Indeed, the reported incidence of VOD is about 20% after allogeneic BMT,[3,4,10] and varies from 4% to 20% after autologous or syngeneic transplants,[3,4,9,11,27,28] with an overall mortality rate of 50%.[5] Our study, including allogeneic and autologous BMT, confirms these results. Eleven of 80 patients (13.6%) in the control group developed VOD, of which seven died due to VOD.

The diagnosis of VOD is based on histologic criteria.[2] However, the histologic confirmation of VOD after BMT is difficult while the patient is still alive and may be hazardous. False-negative liver biopsies have been described in patients later proven to have VOD at autopsy.[2,3,29] Furthermore, marrow aplasia causing thrombocytopenia and coagulopathy due to liver disease may be contraindications to the liver biopsy at an early stage of the disease. Thus, McDonald et al have proposed clinical criteria of VOD after BMT with positive and negative predictive values of 88.5% and 92%, respectively.[4] Jones et al, in a retrospective analysis of liver biopsy or autopsy, confirmed the accuracy of these clinical criteria.[3] Similar conclusions can be drawn from our study because VOD was histologically confirmed in 9 of 10 patients with clinical VOD undergoing liver biopsy. Thus, we believe that clinical presentation of VOD during the first month post-BMT is specific enough to avoid liver biopsy in most cases.

Endothelial injury of terminal hepatic and sublobular central venules due to conditioning chemoradiotherapy appears to be a primal event in the genesis of VOD after BMT.[13,17] Indeed, the endothelium of the hepatic venules and sinusoids was shown to be more sensitive to radiation than hepatocytes.[15,16] Furthermore, endothelial damage is reported to be the earliest morphologic change in chemotherapy-induced VOD in experimental models.[12-14] Shulman et al showed that the endothelial damage was associated with fibrin deposition in the subendothelial zone of the affected venules and surrounding sinusoids early in the genesis of VOD.[17] The events resulting in fibrin deposition remain to be elucidated. Stasis from decreased sinusoid blood flow and endothelial ulceration-induced coagulation are probably involved.[17] Release of tissue thromboplastins from damaged hepatocytes may also trigger the coagulation cascade.[17] A shift in the endothelial hemostatic surface properties favoring clot formation over anticoagulation has also been implied. Indeed, a decrease in the natural anticoagulants (protein C, protein S, antithrombin III) was shown to be coincident with the described peak incidence of VOD after BMT.[30] A decrease in protein C and antithrombin III was found to preceed the overt clinical onset of VOD.[31] Furthermore, tumor necrosis factor, closely associated with early complications of BMT such as endothelial leakage syndrome and VOD,[32] has been shown to increase the procoagulant and decrease the anticoagulant properties of vascular endothelium through the decrease of protein C activation and tissue-type plasminogen activator production.[33] Finally, endothelial injury and the activation of the coagulation cascade induce a pronounced effect on intrasinusoidal flow and pressure that leads to additional damage to hepatocytes surrounding the terminal venules.

To prevent the early deposition of clotting proteins within the terminal hepatic venules, the prophylactic use of anticoagulants appears to be a logical approach. Two provisional reports have suggested that low-dose heparin may decrease the incidence of VOD after BMT. Cahn et al[18] observed only one case of VOD in 63 patients treated with a continuous infusion of low-dose heparin after autologous BMT (100 U/kg/d). In a subsequent study, Rio et al confirmed these results.[19] The efficiency of heparin for the prevention of VOD after BMT was shown in our controlled trial. Only 2 of the 80 patients in the heparin group developed VOD, as compared with 11 of 81 in the control group ($P < .01$). Heparin was also found to delay the onset

of VOD ($P < .01$). Furthermore, the VOD in two patients of the heparin group occurred after heparin interruption, without hepatic dysfunction at the time of interruption. None of the 39 patients who received allogeneic BMT in the heparin group developed VOD, as compared with 7 of 38 in the control group ($P < .01$). This result suggests that patients undergoing allogeneic BMT may preferentially benefit from heparin prophylaxis. However, it has to be considered that our patients were prepared for BMT with a conventional radiochemotherapy regimen. Also, most of these patients underwent BMT at an initial phase of their primary disease. Therefore, whether or not heparin may achieve such a prophylactic effect in patients with advanced disease and/or prepared for BMT with a more intensive regimen remains to be answered.

A major consideration in heparin administration after BMT is the potential risk of bleeding. Bearman et al, in a pilot study, administered four doses of heparin by continuous infusion in 28 patients undergoing BMT.[34] They concluded that a dose of 150 U/kg/d may be infused with a low risk of serious bleeding. However, 21 of 28 patients enrolled in Bearman's study were withdrawn from heparin because of minor bleeding or because of "anticipated bleeding." In our trial, the lower dose of heparin used (100 U/kg/d) was shown to be safe. No major bleeding occurred in the heparin group and the full course of heparin was administered in 77 of 80 patients. Furthermore, our heparin regimen did not prolong PTT and did not increase red blood cell transfusion requirements. Heparin-induced thrombocytopenia is another possible adverse event of such a prophylactic strategy.[35] Its incidence is difficult to clinically assess in the post-BMT setting, and because no reliable laboratory test exists we could not address this issue. However, our study shows that heparin does not increase the mean duration of thrombocytopenia, the mean number of platelet transfusions, and the number of patients refractory to platelet transfusions. Therefore, the contribution of possible heparin-induced thrombocytopenia to platelet support problems was virtually null in our trial.

In conclusion, continuous infusion of low dose heparin was found to be highly effective in preventing VOD after BMT. Such a prophylaxis was achieved without added risk of bleeding. The heparin regimen we used (100 U/kg/d) did not prolong the PTT and did not increase the red blood cell and platelet requirements after BMT. On the basis of these findings, we recommend that heparin be a part of early mortality prevention programs after BMT.

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